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Time for a change — novel options in the 1st line treatment of ALK-positive non-small-cell lung cancer

Last few months brought important new data regarding treatment of anaplastic lymphoma kinase (ALK) non-small-cell lung cancer (NSCLC). Crizotinob — former standard of 1st line treatment — gained potent competitors in ceritinib and alectinib. Despite the fact, that ALK-rearrangements are found only in about 5% of patients with NSCLC, exceptional results obtained with ALK inhibitors justify extensive attention given to this field.

On the 23rd January 2017, Soria et al. [1] reported in The Lancet results from randomized, open-label, phase 3 ASCEND-4 trial, comparing ceritinib and platinum-based chemotherapy in the 1st line treatment of patients with advanced NSCLC harboring ALK-rearrangement. Ceritinib, compared to crizotinib, exhibits more potent inhibition of ALK tyrosine kinase and is more likely to cross the blood-brain barrier. Nonetheless, in ASCEND-4 trial, as it was initiated before introduction of crizotinib into clinical practice, ceritinib was compared with platinum-based doublet chemotherapy (cisplatin or carboplatin with pemetrexed). The trial randomized 376 patients, about 30% of whom had intracranial metastases, in 1:1 ratio to both arms. After the median observation duration of 19.7 months, the study met its' primary end point of improved progression free survival (PFS) in independent review — median PFS was 16.6 months (95% CI 12.6–27.2) in the ceritinib arm and 8.1 months (95% CI 5.8–11.1) in the chemotherapy arm; it resulted in hazard ratio (HR) of 0.55 (95% CI 0.42–0.73; p = 0.00001). The difference remained significant in most of the predefined subgroups. Due to the immaturity of data, the difference in median overall survival (mOS) has not reached statistical significance, despite strong trend towards superiority of ceritinib (HR 0.73; 95% CI 0.50–1.08; p = 0.056). Results in both overall response rate (72.5% *vs*. 50%) and median duration of response (23.9 months *vs*. 11 months), preferred the experimental arm. However, rates of grade 3 and 4 adverse events were higher in the ceritinib group (78% *vs*. 62%) as well as rates of grade 3 and 4 adverse events suspected to be related to the study drug (65% *vs*. 40%). The higher rates of adverse events have not resulted in increased rates of treatment discontinuation due to toxicity (5% in ceritinib arm *vs.* 11% in chemotherapy arm). Additionally, treatment with ceritinib resulted in the prolongation of the time to definite deterioration, improvement in lung cancer-specific symptoms and better results in some parts of the quality-of-life assessment.

Other interesting data regarding the 1st line treatment of patients with advanced ALK-positive NSCLC came from ALEX trial, published on the 6th of June 2017 in The New England Journal of Medicine by Peters et al. [2], which compared the standard-of-care crizotinib with novel, selective ALK-inhibitor alectinib. Contrary to crizotinib, alectinib show high CNS affinity and exhibit activity in the setting of acquired resistance to ALK inhibitors. ALEX trial was phase 3, open label study, that randomized 303 patients, in 1:1 ratio to both of arms, with investigator assessed PFS as the primary end point. About 40% of randomized patients presented with metastases to central nervous system. After the median duration of follow-up 17.6 months in the crizotinib arm and 18.6 months in the alectinib arm, the primary end point was met. In the alectinib arm median PFS was not reached (95% CI 17.6–not estimable) and reached 11.1 months in the crizotinib arm (95% CI 9.1–13.1), with HR of 0.47 (95% CI 0.34–0.65; p < 0.001). Results were consistent in nearly all subgroups analyzed and were confirmed by the independent review (median PFS 25.7 months in the alectinib arm vs 10.4 months in the crizotinib arm, with HR 0.5 (95% CI 0.36–0.70; p < 0.001)). Also, alectinib showed superiority in intracranial disease control (as it significantly lowered 12-month cumulative incidence rate of CNS progression — 9.4% in alectinib arm *vs.* 41.4% in crizotinib arm), in terms of the response rate (82.9% *vs*. 75.5%; p = 0.09) and the duration of response (not estimable *vs.* 11.1 months; HR 0.36). At the data cut-off, the mOS was not estimable in either group. In the safety analysis, alectinib treatment resulted in the significant reduction of gastrointestinal toxicity (nausea 14% *vs.* 48%, diarrhea 12% *vs.* 45% and vomiting 7% *vs.* 38%), at the price of increased rates of anemia (20% *vs.* 5%), myalgia (16% *vs.* 2%) and hyperbilirubinemia (15% *vs.* 1%). Rate of grade 3–5 adverse events was 41% in patients receiving alectinib and 50% in patients receiv-

Oncology in Clinical Practice 2017, Vol. 13, No. 1, 34–37, DOI: 10.5603/OCP.2017.0006, Copyright © 2017 Via Medica, ISSN 2450–1654

ing crizotinib. Adverse events leading to the treatment discontinuation were 11% and 13%, respectively, for alectinib and crizotinib.

As a result of presented trials, three ALK inhibitors (crizotinib, ceritinib and alectinib) are available in 1st line treatment of ALK-positive NSCLC. Available results endorse superiority of alectinib over crizotinib and suggest, in the indirect comparison, higher potency of ceritinib when compared to crizotinib. However, the direct comparison of activity of alectinib and ceritinib in 1st line setting is currently impossible. Safety profile slightly favor alectinib, but despite higher rates of adverse events in patients receiving ceritinib, rates of discontinuation were similar for both of the drugs. In the end, the choice between alectinib and ceritinib remains inconclusive and awaits further, more robust, evidence.

Preoperative radiotherapy for rectal cancer — does timing matter?

Current patterns of preoperative care for rectal cancer include long-course radiotherapy lasting 5–6 weeks of 1.8–2 Gy per fraction radiation, with or without concurrent chemotherapy, and surgery thereafter, and short-course radiotherapy, consisting of five 5 Gy fractions and surgery performed within a week after finishing radiation. Several modified schedules currently undergo evaluation, such as combination of short-course radiotherapy with consolidation chemotherapy [3], and novel results has been recently published.

Stockholm III trial [4] was randomized, phase 3 non-inferiority study, comparing three radiotherapy regimens in the preoperative setting for rectal cancer: standard long-course schedule 25 × 2 Gy, short-course schedule 5 × 5 Gy with a surgery within a week and short-course schedule with a surgery delayed for 4–8 weeks. The primary end point was time to local recurrence and secondary end points included data regarding OS and complications (both of radiotherapy and surgery). Due to investigators preferences towards short-course regimens and logistical reasons, during the trial protocol was amended to include choice of the randomization between only short-course regimens and between all three arms. Overall, 385 patients were randomized between all three arms and 455 patients between two short-course regimens. After the median follow up time of 5.2 years, no significant difference between treatment groups was noted in terms of the local recurrence, incidence of the distant metastases and the overall survival, with low rates of local recurrence in all arms. Among patients randomized between all tree arms, the 5-year recurrence free survival was 65% (95% CI 56–73) in patients receiving standard short-course radiotherapy, 64% (95% CI 54–71) in patients receiving short-course radiotherapy with delayed surgery and 65% (95% CI 56–73) in patients receiving long-course radiotherapy. No significant differences between secondary end points were seen. In the pooled analyses comparing patients receiving short-course radiation with and without delayed surgery from both randomizations, no difference was seen in the primary end point of local recurrence, as well as in the incidence of distant metastases and the any cause mortality. 5-year recurrence free survival was 65% (95% CI 60–70) in patients receiving standard short-course radiotherapy and 68% (95% CI 62–73) in patients receiving short-course radiotherapy with delayed surgery. However, lower rates of postoperative complications were seen in patients receiving delayed surgery (HR 0.61; 95% CI 0.45–0.83; $p = 0.001$) at the cost of higher rate of radiation toxicity, mostly diarrhea and abdominal pain (HR 24.67; 95% CI 3.31–183.72; $p < 0.0001$).

Data from Stockholm III trial confirmed non-inferiority of delayed surgery after short-course radiotherapy in preoperative setting of rectal cancer and established this regimen as a valid option of care. Despite higher rates of radiation toxicity, modified regimen resulted in significantly lower rates of postoperative complications. Further research should asses value of addition chemotherapy to short-course radiotherapy with delayed surgery. Until then, delayed surgery remains valuable option and could be especially considered in patients with modifiable risk factors for perioperative complications.

Angiotensin-converting enzyme inhibitors and b-blockers in the prevention of trastuzumab-associated cardiotoxicity — results from MANTICORE 101-Breast trial

As modern oncology improve cancer patients prognosis and long-term survival, concerns regarding therapy associated toxicities rise. Trastuzumab in the adjuvant setting of HER-2 positive breast cancer gives a good example, as significantly improved outcomes come at the cost of an increased risk of left ventricular dysfunction and symptomatic heart failure. Despite scarce data about prevention of this detrimental process, growing body of evidence provide useful insight into possible pharmacological interventions.

Such evidence has come from MANTICORE 101-Breast trial, which was published on the 10th of March 2017 in the Journal of Clinical Oncology by Pituskin et al. [5]. The trial evaluated effects of either perindopril, bisoprolol or placebo on indexed left ventricular volume (LVEDi; primary end point) and left ventricular ejection fraction (LVEF; secondary end point) during trastuzumab-based adjuvant therapy for early breast cancer. In total, 94 patients, of whom 77% received a non-anthracycline based chemotherapy concurrently with trastuzumab, were randomized to all three arms in 1:1:1 ratio. After median observation time of 350 days, the study failed to meet the primary end point. Change in LVEDi was similar between arms, with mean of +4 ± 11 mL/m^2 in the placebo group, +7 ± 14 mL/m^2 in the perindopril group and +8 ± 9 mL/m^2 in the bisoprolol group (p = 0.36). However, protective effect of bisoprolol on LVEF was seen, when compared to placebo and perindopril arms (–1 ± 5% *vs.* –3 ± 4% and –5 ± 5%, respectively; p = 0.001). Also, fewer patients in both intervention arms had trastuzumab therapy interruptions (3 of 33 in the perindopril group and 3 of 33 in the bisoprolol group, in contrast to 9 of 30 in the placebo group; p = 0.03). In the multivariable analysis, prevention of a decline in LVEF was seen with use of perindopril (p = 0.016) and bisoprolol (p < 0.001). No significant drug-related adverse effects or serious adverse events were reported.

Presented study addresses crucial lack of evidence in the area of trastuzumab cardiotoxicity prevention. Despite failing to meet the primary end point of attenuating ventricular remodeling, results regarding LVEF preservation and fewer treatment interruptions suggest modest protective effects of bisoprolol and, less significantly, perindopril. This opportunity of introducing safe, inexpensive and accessible modality for prevention of trastuzumab-associated cardiotoxicity should be validated in further studies.

Efficiency of radiolabeled somatostatin analogue therapy in progressive neuroendocrine tumors originating from midgut — is ^{177}Lu-Dotatate the new standard?

When compared to other solid tumors, well-differentiated neuroendocrine tumors of midgut are characterized with preferable prognosis and long-term survival. Nevertheless, standard first-line systemic therapy in this setting, somatostatin analogue, has limited antitumor activity and second-line options are limited mostly to everolimus and cytotoxic therapy. As many of the well differentiated neuroendocrine tumors express somatostatin receptors, concept of labeling somatostatin analogues with radionuclides to deliver intratumoral radiation seemed promising option, with encouraging results from early phase trials.

The results of NETTER-1 trial, were published by Strosberg et al. [6] on the 12th of January 2017 in The New England Journal of Medicine. It was randomized phase 3 trial comparing ^{177}Lu-Dotatate and octreotide long-acting repeatable (LAR) versus high-dose LAR monotherapy in patients with progressive well-differentiated (defined as exhibiting Ki67 index of 20% or less), somatostatin receptor-positive, neuroendocrine tumors of midgut. Patients in the experimental arm received up to four applications of ^{177}Lu-Dotatate at a dose of 7.4 Gbq each, given every 8 weeks. The study randomized 229 patients in 1:1 ratio to both of arms, with the primary end point of PFS and secondary end points of objective response rate, OS, safety and profile of side-effects. At the data cut-off, the median PFS was not reached in the ^{177}Lu-Dotatate group and was 8.4 months in the placebo group, with HR of 0.21 (95% CI 0.13–0.33; p < 0.001). The experimental arm also showed superiority in the rate of PFS at month 20 — 65.2% (95% CI 50.0–76.8) *vs.* 10.8% (95% CI 3.5–23.0) and in the response rate — 18% *vs.* 3% (p < 0.001). Beneficial effects of ^{177}Lu-Dotatate were seen in all analyzed subgroups, independently from prognostic factors. In a planned, interim analysis of OS, data were immature and threshold for significance have not yet been reached. In the safety analysis, any treatment-related adverse events occurred in 86% of patients receiving ^{177}Lu-Dotatate and 31% of patients receiving high-dose LAR, with grade 3–4 events occurring in, respectively, 41% and 33% patients. Nausea, vomiting, diarrhea and hematological abnormalities were the most common adverse events related to ^{177}Lu-Dotatate. However, rate of patients withdrawal from trial due to adverse events was lower in the intervention arm (6%) than in the control arm (9%).

Radiolabeled somatostatin analogues can be recognized as a valid therapeutic option for patients with progressive, somatostatin receptor-positive, neuroendocrine tumors originating from midgut. High value of this therapeutic modality should be attributed to its' excellent efficiency and favorable toxicity profile. Data from interim OS analysis, despite immaturity, are more than promising and could be considered breakthrough, if confirmed in final analysis. Further studies should provide additional insight into appropriate place of the radiolabeled somatostatin analogues therapy, with a presumable potential to become standard of care for somatostatin receptor-positive neuroendocrine tumors.

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